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ORIGINAL RESEARCH CORONA EXPERIENCE

Accuracy of d-dimer in predicting mortality of COVID-19 patients in intensive care unit

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ABSTRACT

Background: Sars-Cov-2 infection has a high rate of mortality. This infection can cause changes in the hemostatic system including activated partial thromboplastin time (aPTT), international normalized ratio (INR), and prothrombin time (PT), increased D-dimer and fibrin degradation product (FDP). D-dimer level in COVID-19 patients affects the mortality rate of COVID-19 patients.

Methodology: This study was a retrospective observational analytic prognostic study using medical record. Inclusion criteria were patients with confirmed COVID-19 who met the criteria for severe and critical pneumonia, aged >18 years who were admitted to RSMH from March 1, 2020 to February 28, 2021, until a minimum of 77 subjects were included. Data analysis was done using SPSS version 26 with chi square to assess the relationship and using the Medcalc to assess area under the curve (AUC), cutoff value, sensitivity and specificity.

Results: There was a total of 91 research subjects and the total mortality rate was 62 (68.1%). The accuracy analysis of D-Dimer on the first day; the cutoff value was 1.79 and the AUC value was 0.556 which has poor predictability. The results of statistical tests using Chi square obtained P value = 0.009 ($p<\alpha$) and Relative Risk 1.991. The accuracy analysis of D-Dimer on the third day, the cut off value was 2.45 and the AUC value was 0.801, which had good predictability. The results of the Chi Square statistical test obtained P value = 0.001 ($p<\alpha$) and Relative Risk 3.157. D-Dimer levels > 2.45 on the third day had a sensitivity value of 90.3% and a specificity of 58.6%. Based on the analysis of the accuracy of the difference in levels of D-Dimer on the first and third day, the Chi Square statistical test results obtained P value = 0.034 ($P < 0.05$) and Relative Risk 1.674.

Conclusion: D-Dimer level > 2.45 was statistically significant associated with mortality and had a risk of 3,157 times in mortality. From the results of the analysis, it was found that the sensitivity, specificity and AUC value were good, so that the third day D-Dimer could be used as a predictor of mortality in sepsis patients.

Abbreviations: AUC - Area Under Curve; aPTT - activated partial thromboplastin time; DIC - disseminated intravascular coagulation; FDP - Fibrin Degradation Product; IL-6 - interleulin-6; INR - International Normalized Ratio; PT - prothrombin time

Keywords: D-Dimer, COVID-19, mortality, activated partial thromboplastin time (aPTT), international normalized ratio (INR), prothrombin time (PT), fibrin degradation product (FDP).

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1. INTRODUCTION

Severe Acute Respiratory Syndrome - Coronavirus 2 (SARS-CoV-2), has caused a global respiratory pandemic known as Coronavirus Disease 2019 (COVID-19), which has rapidly spread across more than 100 countries since its emergence in December 2019.[1] As of June 2021, COVID-19 has infected over 178 million individuals worldwide, with a mortality count of 3.87 million. In Indonesia alone, 2,018,113 people have been diagnosed with the disease, and 55,291 have succumbed to it. Specifically, in South Sumatra, there were 27,381 confirmed cases and 1,384 deaths by the end of June 2021.[2,3] COVID-19 presents with a wide clinical spectrum, ranging from mild to critical cases that require intensive care.[4] The disease manifests through enteric, hepatic, nephrotic, neurological, and cardiac symptoms, leading to multi-organ failure and a high risk of mortality.[5]

While millions have been affected globally, the prognostic factors and treatment regimens for COVID-19 are still not fully defined. Most patients have a favorable prognosis, but some progress to severe or critical cases, developing respiratory distress syndrome, coagulopathy, and multi-organ failure. Patients with COVID-19-related pneumonia exhibit various coagulopathy parameters, which have been linked to higher mortality rates. These hemostatic changes include activated partial thromboplastin time (aPTT), international normalized ratio (INR), prothrombin time (PT), elevated D-dimer levels, and fibrin degradation products (FDP).[6]

The mortality rate of COVID-19 is very high. A study conducted in New York hospitals found 641 COVID-19 cases, with 195 patients in intensive care and 82 deaths. Of these, 34 died after being transferred to the ICU.[7] In a similar study in three Dutch hospitals, the ICU mortality rate for COVID-19 patients was 13%.[8] Another cohort study at Guglielmo da Saliceto Hospital in 2020 reported that 35.1% of ICU patients died within 28 days, with a median death time of 11 days after ICU admission.[9]

Coagulation dysfunction in COVID-19 is marked by Virchow's Triad; endothelial damage, stasis, and hypercoagulability. Endothelial damage results from the direct invasion of cells by SARS-CoV-2, which enters via ACE-2 receptors abundant in endothelial cells. This damage is further exacerbated by an overactive inflammatory response, with elevated cytokine levels like IL-6 and activated complement pathways contributing to endothelial injury. This leads to impaired fibrinolysis and a hypercoagulable state, resulting in increased D-dimer levels and FDP. Excessive intravascular coagulation may cause microthrombi, reducing organ perfusion and leading to multi-organ failure.[10–13]

The severe pro-coagulant state in COVID-19 involves intense inflammatory and coagulation responses.[14] Pro-inflammatory cytokines, such as IL-6, stimulate platelet activation, while mononuclear cells produce tissue factors, triggering the extrinsic coagulation cascade. This results in widespread microthrombi, disseminated intravascular coagulation (DIC), and, particularly in the lungs, acute respiratory distress syndrome (ARDS). Early coagulation abnormalities, like elevated D-dimer and fibrinogen levels, highlight the importance of monitoring hemostasis in COVID-19 patients. High D-dimer levels are associated with worse outcomes, indicating active thrombosis and poor prognosis.[15–17]

The purpose of this study was to determine the accuracy of D-dimer levels in predicting mortality rates among COVID-19 patients at RSMH Palembang. Previous research has shown that D-dimer levels affect mortality in COVID-19 patients.[11,16,18] One study indicated that an initial D-dimer level greater than 2.0 µg/mL (a fourfold increase) could predict in-hospital mortality in COVID-19 patients.[1] Therefore, D-dimer can be a useful early predictor to improve COVID-19 patient management, with elevated levels indicating a worsening clinical condition.

2. METHODOLOGY

2.1. Study Design

This study is a retrospective, observational, prognostic analysis using medical records as the instrument. The research will be conducted in the COVID-19 ICU at Dr. Mohammad Hoesin General Hospital (RSMH) Palembang and the Medical Records Department of the hospital, covering the period from March 2020 to February 2021.

2.2. Study Participants

The study population consists of all adult COVID-19 patients, with the accessible population being adults who were treated in the COVID-19 intensive care unit at Dr. Mohammad Hoesin General Hospital in Palembang during the study period. These patients form the basis for the research, which aims to examine the prognostic value of D-dimer levels in predicting mortality among critically ill COVID-19 patients.

The study sample included those patients who mee specific inclusion and exclusion criteria. The inclusion criteria are patients over 18 years of age, confirmed to have COVID-19, and diagnosed with severe or critical COVID-19-related pneumonia. However, patients with

Table 1: Baseline characteristics

Characteristics	Total n (%)
Age (years) (Min -Max)	52 ±12.888 (21 – 83)
Gender	
- Male	52 (57.1)
- Female	39 (42.9)
Body Mass Index	
- Underweight	5 (5.5)
- Normal	19 (20.9)
- Overweight	25 (27.5)
- Obesity I	32 (35.2)
- Obesity II	10 (11.0)
Comorbids	
- Hypertension	59 (64.8)
- Diabetes mellitus	21 (23.1)
- Heart disease	5 (5.0)
- Cerebrovascular disease	69 (75.8)
- Sepsis	91 (100)
MAP (mmHg)	98.67 (53-142)
SpO_2	96 (52 -100)
SOFA score on ICU admission	9 (4 –16)
Lactate level (IU/L)	2.87 (0.10-23)
ICU length of stay (Days)	9 (3-30)
Length of ventilation support (Days)	7 (3-30)

incomplete medical records, those who died within three days of admission, and those with a history of primary coagulation disorders, such as hemophilia or Von Willebrand disease, are excluded from the study. These criteria help ensure that the study focuses on a relevant and reliable patient group.

2.3. Ethical Statement

This study was approved by the Health Research Ethics Committee of Dr. Mohammad Hoesin General Hospital (RSMH) Palembang (Approval No.121/kepkrsmh/2021 Date: October 21st, 2021). Informed consent was obtained from all individual participants included in the study. Participants were fully informed about the nature, purpose, and potential risks and benefits of the study. Confidentiality of participants was maintained by anonymizing personal data and removing all identifying information from the research records. The study was conducted in compliance with the ethical standards of the The Honorary Council of Medical Ethics of the Indonesian Doctors Association (MKEK IDI) with the 1964 Helsinki Declaration and its later amendments.

2.4. Data Collection

This study examines various variables to understand their impact on COVID-19 patient outcomes in the ICU. The dependent variable is mortality, and the key independent variables include D-dimer levels on the first and third days of ICU treatment, used to evaluate their effect on patient survival.

Subject characteristics assessed include demographic details (initials, age, sex, comorbidity index, Body Mass Index), respiratory parameters (Oxygen Saturation), hemodynamic status (Mean Arterial Pressure), the Sequential Organ Failure Assessment score, lactate levels, and the duration of ICU and ventilator use.

Confounding variables considered include factors such as immobilization, age-related issues, diabetes mellitus, hypertension, heart disease, sepsis, pregnancy, and cerebrovascular disease, which may affect the study outcomes.

D-dimer levels will be used to assess thrombotic events in patients' blood. Measurements will be taken on the first and third days of treatment in the ICU and recorded in micrograms per milliliter (µg/ml). These values will be extracted from medical records and analyzed as a numerical variable.

Comorbidities will be evaluated using the Charlson Comorbidity Index score, which categorizes the severity of pre-existing diseases. This score is derived from medical records and classifies patients into categories based on their comorbid conditions: a score of 0 indicates no comorbidities, 1-2 reflects mild to moderate comorbidities, 3-4 denotes significant comorbidities, and a score above 5 represents severe comorbid conditions. This will be treated as a categorical variable in the analysis. Mortality refers to the outcome of COVID-19 patients during their stay in the intensive care unit (ICU). This is assessed using data from medical records, where mortality is categorized as either 0 or 1. A value of 0 indicates that the patient did not die, while a value of 1 signifies that the patient has died. This variable is treated as categorical.

2.5. Statistical analysis

Data processing and analysis in this study will be conducted using SPSS version 26.0 and Medcalc. Basic characteristic data will be displayed according to the type of variable. For normally distributed numeric variables, data will be presented as mean ± standard deviation (SD), or median (minimum-maximum) if the distribution is not percentages.

Prognostic values of D-dimer will be presented using curves and cutoff values to predict mortality. The Receiver Operating Characteristic (ROC) Curve will be used to calculate the area under the curve (AUC) for D-dimer, evaluating its sensitivity and specificity in

Table 2: Mortality analysis

Characteristics	Mortality Groups		Total n (%)	P-value	RR (95% CI)
	Not survived n (%)	Survived n (%)			
Age (Years)					
18 – 65	53 (66.3)	27 (33.8)	80 (87.9)	0.299*	2.292
> 65 (Geriatric)	9 (81.8)	2 (18.2)	11 (12.1)		(0.463-11.363)
Gender					
Male	35 (67.3)	17 (32.7)	52 (57.1)	0.846*	1.093
Female	27 (69.2)	12 (41.4)	39 (42.9)		(0.447 – 2.670)
Comorbidity Index					
Score 0	12 (66.7)	6 (19.8)	18 (19.8)		
Score 1-2	34 (72.3)	13 (27.7)	47 (51.6)	0.482*	-
Score 3-4	13 (68.4)	6 (31.6)	19 (20.9)		
Score >5	3 (68.1)	4 (57.1)	7 (7.7)		
Body Mass Index					
Underweight	3 (60)	2 (40)	5 (5.5)		
Normal weight	12 (62.2)	7 (36.8)	19 (20.9)		
Overweight	19 (76.0)	6 (24.0)	25 (27.5)	0.591*	-
Obese I	23 (71.9)	9 (28.1)	32 (35.2)		
Obese II	5 (50.0)	5 (50.0)	10 (11.0)		
Hypertension					
Yes	41 (69.5)	18 (30.5)	59 (64.8)	0.705*	0.838
No	21 (65.6)	11 (34.6)	32 (35.2)		(0.335 – 2.095)
Diabetes Melitus					
Yes	18 (85.7%)	3 (14.3)	21 (23.1)	0.049*	3.545
No	44 (62.9)	26 (37.1)	70 (76.9)		(0.952–13.205)
Heart Disease					
Yes	4 (80.0)	1 (20.0)	5 (5.0)	1.000*	0.518
No	58 (67.4)	28 (32.6)	86 (95.0)		(0.055-4.851)
Pregnancy					
Yes	0	0	0	-	-
No	62 (68.1)	29 (31.9)	91 (100)		
Cerebrovascular Disease	51 (73.9)	18 (26.1)	69 (75.8)	0.036*	2.833
Yes	11 (50.0)	11 (50.0)	22 (24.2)		(1.049-7.652)
No					
Immobilization					
Moderate Risk	46 (68.7)	21 (31.3)	67 (73.6)	0.858*	0.913
Mild Risk	16 (66.7)	8 (33.3)	24 (26.4)		(0.338-2.465)
Ventilation Type					
Ventilator	62 (93.9)	4 (6.1)	66 (72.5)	0.001*	-
HFNC	0 (0)	3 (100)	3 (3.3)		
NIV	0 (0)	22 (100)	22 (24.2)		
Sepsis					
Yes	62 (68.1)	29 (31.9)	91 (100)	-	-
No	0	0	0		

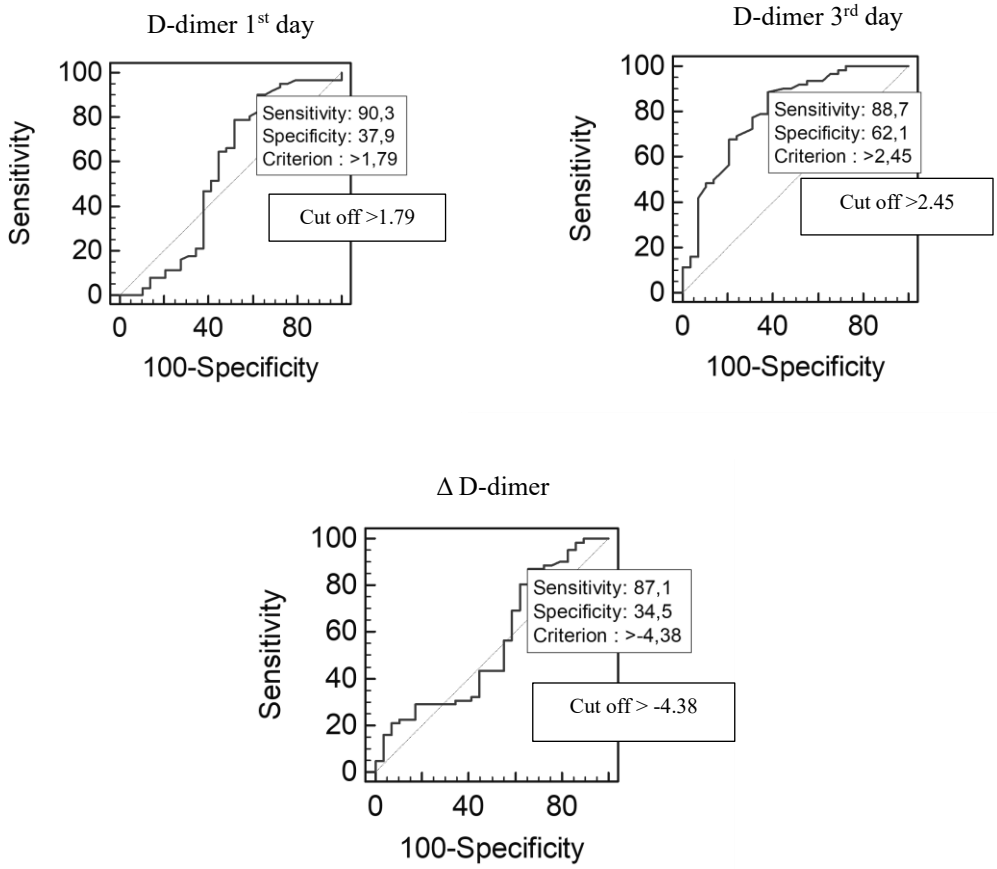

Figure 1: Day 1st, 3rd and ΔD-dimer ROC analysis

predicting COVID-19 mortality. Additionally, the study will analyze the difference in AUC between D-dimer levels on the first and third days in relation to mortality.

Statistical significance will be determined using P-values, with $P \leq 0.05$ indicating significance and $p > 0.05$ indicating non-significance.

3. RESULTS

The baseline characteristics of the study subjects are categorized by age, sex, body mass index (BMI), and comorbidity index as presented in Table 1. Descriptive analysis shows that the average age of COVID-19 patients in the ICU is 52 ±12.888 yr, with ages ranging from 21 to 83 years. There are 52 male subjects (57.1%) and 39 female subjects (42.9%). Among BMI categories, the most common group is Obesity I, with 32 subjects (27.5%). The most frequent comorbid conditions are cerebrovascular disease, affecting 69 subjects (75.8%), and hypertension, affecting 59 subjects (64.8%). The median ICU stay duration is 9 days, with a range from 3 to 30 days, and the median duration of ventilator use is 7 days, also ranging from 3 to 30 days.

Table 2 shows that 66.3% of those aged 18-65 and 81.8% of those over 65 died. The Chi-Square test showed that age and gender are not statistically significant for mortality, with the 18-65 age group having a slightly higher risk, but men and women having the same risk.

The study showed that the majority of participants had a comorbidity index of 1-2, with 47 subjects (51.6%), and 34 of them (72.3%) died. The Chi-Square test indicated no significant statistical link between the comorbidity index and mortality ($P = 0.482$). However, cerebrovascular disease was significantly related to higher mortality, with a P-value of 0.036 and an RR of 2.833, meaning those with the disease had a 2.8 times higher risk of death. The study also found increased mortality rates among patients with hypertension, diabetes, or heart disease, but only cerebrovascular disease showed statistical significance.

The study found that most patients had a moderate risk of immobility according to the Braden Scale, with 67 subjects (73.6%), compared to 24 subjects (26.4%) at

Table 3: Multivariate analysis

Variable	B	Constant	P-value	RR	Confidence Interval 95%	
					Lower	Upper
3rd Day D-Dimer	1,671	-4,016	0,000	5,039	0,519	15,028

mild risk. Among those at moderate risk, 46 (68.7%) died, compared to 16 (66.7%) in the mild risk group, with no significant statistical difference (P = 0.858). Regarding ventilation support, 66 patients (72.5%) used a ventilator, 22 (24.2%) used Non-Invasive Ventilation, and 3 (3.3%) used a High Flow Nasal Cannula. Of those on ventilators, 62 (63.9%) died, with a statistically significant association between ventilator use and mortality (P = 0.001).

The study found that D-Dimer levels on the first day showed a non-normal data distribution, with a median of 3.82 (range 0.42–12.24). Using ROC curve analysis, the cut-off point for D-Dimer as a predictor of mortality in COVID-19 patients in the intensive care unit was identified as >1.79, with an AUC of 0.556, indicating it as a poor predictor. On the third day, D-Dimer levels also showed a non-normal distribution, with a median of 3.20 (range 2.12–9.12). The ROC curve analysis revealed an AUC of 0.801 and a cut-off point of >2.45, indicating it as a good predictor of mortality.

Table 3 shows that D-Dimer levels on day one with a cut-off point >1.79 showed that 74.7% of patients with levels >1.79 died, compared to 37.5% of those with levels <1.79, with a significant P-value of 0.009. The relative risk (RR) was 1.991, indicating that patients with D-Dimer >1.79 were 1.991 times more likely to die, with a sensitivity of 90.3% and specificity of 34.5%. On day three, using a cut-off > 2.45, 82.4% of patients with levels >2.45 died, with a P-value of 0.001, RR of 3.157, sensitivity of 90.3%, and specificity of 58.6%. A decrease in D-Dimer levels by >4.38 between days one and three was also linked to mortality, with 74.0% of these patients dying (P-value = 0.034, RR = 1.674), with a sensitivity of 87.1% and specificity of 34.5%.

A multivariate analysis using binary logistic regression was conducted to identify the most dominant factors affecting COVID-19 patient mortality. The analysis included confounding variables such as age, BMI, gender, comorbidities (diabetes, hypertension, heart disease, CVD), and immobilization, along with D-Dimer levels on the first and third days. Using the Backward LR method, the third-day D-Dimer level emerged as the most dominant predictor of mortality in COVID-19 patients.

4. DISCUSSION

Our study found that the majority of subjects were aged 18-65 years (87.9%), compared to those over 65 years (12.1%), due to the broader age range of 18-65 years. The older age group had a higher mortality rate (81.8%), aligning with theories that COVID-19 mortality risk increases with age.19,20 The average age of deceased patients was 57.44 years, while survivors averaged 42.8 years.[2]1 Elderly patients often experience reduced physical mobility and increased hospitalization, contributing to hypercoagulation. Meta-analyses show that severe COVID-19 cases have older median ages compared to mild cases.[22] Studies also indicate that VTE incidence rises with age, and patients aged ⩾65 years show elevated coagulation and inflammation markers. Older age is an independent predictor of mortality in SARS and MERS cases, likely due to weaker immune responses. [23,24]

The study found that male subjects were more prevalent (57.1%) compared to female subjects (42.9%). Statistical analysis showed no significant difference in mortality risk between genders (P-value 0.846, RR 1.093). This aligns with previous studies by Soni et al.[20] and Poudel et al.[19], which also found no significant difference in mortality risk between genders despite higher male incidence rates. The lower susceptibility of females to COVID-19 is attributed to protective factors like the X chromosome and sex hormones, which play crucial roles in both innate and adaptive immunity. Lifestyle differences, such as higher smoking rates and comorbidities in males, may also contribute.[19,20]

The distribution based on comorbidity index shows that most patients (72.3%) had a comorbidity index of 1-2, with the same percentage for mortality rates. Studies indicate that comorbidities increase the prediction of mortality by 10.3% (CI: 6.8% - 13.4%) compared to those without comorbidities or with a score below 2. Comorbid factors can also predict a 12% chance of COVID-19 becoming more severe.20 Previous research by Soni et al.20 found that cerebrovascular disease has the highest prognostic value for mortality in COVID-19 patients (12.6%), followed by cardiovascular disease (7.5%), arterial hypertension (6%), diabetes (5.6%), and obesity (1.41%). Hypertension was common in this study, but not the most influential factor for mortality in ICU patients.[19] Further research is needed to explore the link between diabetes and mortality in ICU COVID-19 patients, while obesity increases ICU admission risk without significantly raising mortality. Obesity can worsen COVID-19 outcomes by increasing ACE2 and CD147 expression, making patients more vulnerable to infection and potential organ dysfunction.[25]

The median length of stay in the ICU was 9 days, with a minimum of 3 days and a maximum of 30 days. Similarly, the median duration of ventilator support was 9 days, ranging from 3 to 30 days. Of the patients requiring respiratory support, 72.5% (66) used a ventilator, while 3.3% (3) used a High Flow Nasal Cannula (HFNC) and 24.2% (22) used Non-Invasive Ventilation. Among those using ventilators, 63.9% (62) died, while there were no deaths among those using other respiratory aids. This study's findings on the duration of mechanical ventilation align with previous research, which also reported a median of 9 days and a COVID-19 ICU mortality rate of 25.6%.[26]

The median SOFA score was 9 (range: 9 to 16), with all patients diagnosed with sepsis based on this score. The median lactate level was 2.87 (range: 0.10 to 12). Clinically, an increase of 2 or more points in the SOFA score is associated with a higher than 10% in-hospital mortality rate. Previous research indicates that older age (OR 1.10, 95% CI 1.03-1.17, per year; P = 0.0043) and higher SOFA scores (OR 5.65, 95% CI 2.61-12.23; P < 0.0001) are linked to increased hospital mortality. Combining a high SOFA score with D-dimer > 1 g/mL can help identify poor prognosis in COVID-19 patients early. The SOFA score, part of the Sepsis-induced Coagulopathy (SIC) score, can also identify patients who might benefit from intensive thromboprophylaxis. Tang et al. found that patients with a SIC score of 4 or D-dimer > 3 g/mL (six times the upper normal limit) had significantly lower 28-day mortality rates (40.0% vs. 64.2%, P = 0.029 and 32.8% vs. 52.4%, P = 0.017) when treated with UFH or LMWH.[27]

The ROC curve analysis for D-Dimer levels on the first day showed an AUC of 0.556, with a cut-off point of 1.79. This indicates that a D-Dimer level of 1.79 is a predictor of poor outcomes for COVID-19 patients in the ICU. Statistical testing revealed a P-value of 0.009 ($p < \alpha$) and a Relative Risk of 1.991, meaning patients with D-Dimer >1.79 are statistically significantly more likely to die, being 1.991 times more at risk compared to those with levels below 1.79. D-Dimer >1.79 on the first day has a sensitivity of 90.3% and a specificity of 34.5% for predicting death. Previous study found that non-survivors had higher D-Dimer levels (median 4.6 g/mL) compared to survivors (median 0.6 g/mL).22 Zhou et al.28 identified D-Dimer >1 g/mL as the best mortality predictor with an odds ratio of 18.42 (95% CI 2.64-128.55; P = 0.0033). Zhang et al.1 reported an optimal cut-off of 2.0 mg/mL with 92.3% sensitivity and 83.3% specificity for predicting in-hospital mortality, whereas Soni et al.20 found that a D-Dimer level of 1.44 mg/mL within 24 hours had a sensitivity of 60.5% and specificity of 74.0%, indicating it was not a strong mortality predictor in their study.

The ROC curve analysis for D-Dimer levels on the third day revealed an Area Under the Curve (AUC) of 0.801, with a cut-off point of >2.45. This suggests that a D-Dimer level above 2.45 on day three is a good predictor of mortality for COVID-19 patients in the ICU. The Chi-Square test showed a P-value of 0.001 ($P < \alpha$) and a Relative Risk of 3.157, indicating that patients with D-Dimer >2.45 are 3.157 times more likely to die compared to those with levels below 2.45. This level of D-Dimer has a sensitivity of 90.3% and a specificity of 58.6% for predicting death.

In contrast, the ROC analysis for the difference in D-Dimer levels between the first and third day yielded an AUC of 0.551, with a cut-off point of >-4.38. This suggests that the change in D-Dimer levels is a poor predictor of mortality. The Chi-Square test for this difference showed a P-value of 0.034 ($P < \alpha$) and a Relative Risk of 1.674, meaning patients with a D-Dimer difference > -4.38 are 1.674 times more likely to die compared to those with a difference ⩽-4.38. The difference in D-Dimer levels > -4.38 has a sensitivity of 87.1% and a specificity of 34.5%.

This study also analyzed independent variables (D-Dimer levels on the first and third day) and confounding variables (age, BMI, gender, comorbidities, diabetes, hypertension, heart disease, cerebrovascular disease, immobilization) in predicting COVID-19 mortality using Backward LR. The results indicated that only the D-Dimer level on the third day was the most dominant predictor of mortality (P-value 0.001; RR 5.039; 95% CI 0.519-15.028).

D-Dimer is a protein resulting from fibrin degradation, found in blood after clot dissolution (fibrinolysis). The term "D-Dimer" refers to the presence of two D fragments of the fibrin protein linked by a cross-link. Elevated D-Dimer levels in COVID-19 reflect inflammation, endothelial damage, and hypercoagulation. Intravascular hypercoagulation leads to fibrin deposition, which eventually breaks down through fibrinolysis, increasing D-Dimer and FDPs levels.[11,29,30]

In this study, the D-Dimer level on the first day was not a strong predictor of mortality. The positive predictive values for D-Dimer levels on the first day, third day, and their difference were 74.67%, 82.35%, and 73.97%, respectively. Variations in disease onset, morbidity, and severity among patients affect mortality rates. Significant morbidities influencing mortality in this study included cerebrovascular history, diabetes mellitus, and sepsis, with mortality rates of 73.9% and 85.7% for these conditions, respectively. A limitation of this study was incomplete data on patient treatment histories.

D-Dimer levels on the third day were a better predictor of mortality (AUC 80.1%), likely due to the administration of appropriate interventions such as anti-inflammatory drugs, anticoagulants, and antibiotics based on COVID-19 management guidelines. This results in a more accurate predictive value compared to the first day. The change in D-Dimer levels from day one to day three was also assessed to observe hypercoagulation response after treatment. A decrease in D-Dimer levels greater than 4.38 on day three was significantly associated with mortality, suggesting that targeting a reduction in D-Dimer levels of more than 4.38 is beneficial. The study's limitation includes the lack of complete treatment data.

In severe SARS-CoV-2 infections, uncontrolled innate inflammation and disrupted adaptive immune responses are reflected in elevated serum pro-inflammatory cytokines such as IL-6, IL-1, IL-2, IL-8, IL-17, G-CSF, GM-CSF, IP10, MCP1, MIP1α, and TNF. This inflammation interacts with coagulation processes, leading to increased expression of tissue factor (TF) on endothelial cells and monocytes, thereby promoting procoagulant activity. Autopsy reports of COVID-19 patients reveal widespread neutrophil infiltration in pulmonary capillaries, acute capillaritis, and fibrin deposition, suggesting that neutrophil extracellular traps (NETs) contribute to organ damage and thrombosis. Hypoxia further exacerbates procoagulant activity by upregulating hypoxia-induced transcription factors that modulate coagulation and fibrinolysis factors.[22] Elevated D-Dimer levels, associated with pathological conditions like venous thromboembolism and infections, also indicate increased fibrin production or degradation. In COVID-19, dysregulation of the coagulation/anticoagulation cascade worsens lung pathology, similar to the pathological findings seen in other viral infections such as influenza, including diffuse alveolar damage, cellular exudates, pneumocyte desquamation, and interstitial mononuclear infiltrates dominated by lymphocytes.[31–33]

This study aligns with research by Soni et al.20, showing that D-Dimer levels on the third day are better predictors of mortality compared to day one. Specifically, day one D-Dimer had poor predictive value for mortality (cutoff 1.44 µg/ml, ROC 0.683; sensitivity 60.5%; specificity 74.0%), whereas day three levels were more reliable (cutoff 2.01 µg/ml, ROC 0.789; sensitivity 73.3%; specificity 70%). In contrast, Creel-Bulos et al.[34] found that changes in D-Dimer levels were predictive of VTE but not mortality. Huang et al.[35] indicated that elevated D-Dimer levels upon admission were associated with increased mortality and higher intensive care needs, supporting recommendations for hospitalization based on D-Dimer increases. Poudel et al.[19] identified an optimal cutoff of 1.5 µg/ml for mortality prediction, while Zhang et al.[36] suggested a cutoff of ⩾2.0 µg/ml for the first 24 hours post-admission. Al-Samkari et al.[37] also found that prophylactic anticoagulation improved outcomes in COVID-19 patients with elevated coagulation markers.

Increased D-dimer levels indicate hypercoagulation in COVID-19 patients, potentially due to several factors. Firstly, the virus often triggers an aggressive inflammatory response and inadequate anti-inflammatory control, leading to endothelial dysfunction and excessive thrombin formation. Secondly, severe COVID-19-induced hypoxia can stimulate thrombosis through blood viscosity changes and hypoxia-induced transcription factor pathways. Thirdly, hospitalized patients, especially those with severe symptoms, are at higher risk for hypercoagulation due to age, underlying conditions, prolonged immobilization, and invasive treatments. Autopsies of critically ill COVID-19 patients have shown pulmonary microthrombi and occlusions. Additionally, some patients may develop sepsis-induced coagulopathy or disseminated intravascular coagulation. Although elevated D-dimer is associated with adverse outcomes, its low specificity can be a limitation, though it can also be useful in prognosis evaluation. The positive predictive values for D-dimer on days one, three, and the change between them are 74.67%, 82.35%, and 73.97%, respectively, while the negative predictive values are 62.50%, 73.91%, and 55.55%. Asghar et al.[38] found different predictive values for D-dimer at admission and discharge, highlighting the need for further research with larger sample sizes to resolve these discrepancies.

5. LIMITATIONS

This study has several limitations, including its retrospective nature, which introduces potential biases. The diverse backgrounds and varying onset of illness among patients may affect initial D-Dimer levels. Additionally, the lack of data on comorbid variables may result in less accurate determinations of the causes of mortality.

6. CONCLUSION

D-Dimer levels on the third day have shown better predictive accuracy for mortality compared to levels on the first day and the difference between D-Dimer levels on the first and third days. D-Dimer levels on the first day had poor predictability for mortality (cut-off >1.79, AUC 0.556, sensitivity 90.3%, specificity 34.5%). In contrast, D-Dimer levels on the third day were a good predictor of mortality (cut-off 2.45, AUC 80.1%, sensitivity 90.3%, specificity 58.6%). The difference in D-Dimer levels between the first and third days had poor

predictive value for mortality (cut-off >4.38, AUC 0.551, sensitivity 87.1%, specificity 34.5%).

7. RECOMMENDATIONS

We suggest further experimental studies to explore the correlation between therapy and D-dimer levels in research subjects. Additionally, performing studies with repeated D-dimer measurements across two or more groups can provide more comprehensive information. It is also suggested to investigate D-dimer levels as a mortality predictor in conjunction with clinical comorbidities and other laboratory parameters for COVID-19 patients.

8. Conflict of Interest

The authors declare that they have no conflict of interest.

9. Authors contribution

1. HH, concept, conduction of study work, and manuscript editing.

2. RM, concept and reviewing the research and manuscript.

3. MIL, concept and reviewing the research

4. EB, reviewing the research

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